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(54) Transdermal compositions containing Nimesulide

(57) Novel therapeutic anti-inflammatory and analgesic compositions are disclosed containing Nimesulide, i.e. N-(4-nitro, 2 phenoxyphenyl) methane sulphonamide for use transdermally, also a process for their preparation.

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Description

TECHNICAL FIELD

This invention relates to novel therapeutic anti-inflammatory and analgesic pharmaceutical compositions containing Nimesulide which is N-(4 nitro, 2 phenoxyphenyl) methane sulphonamide for use transdermally and a process for the manufacture thereof.

BACKGROUND OF THE INVENTION

For a drug to be absorbed transdermally, it has to travel through various layers of the skin before reaching the site of action.

The layers of the skin are different in nature, some are hydrophilic while some are lipophilic (Montagna W. Parrakhal PF: The structure and Function of the skin, 3rd ed. Academic press, New York, 1974). Accordingly, any drug which is used transdermally must possess both hydrophilic and lipophilic properties. Nimesulide which is N-(4 nitro, 2 phenoxyphenyl) methane sulphonamide, is a highly hydrophobic drug and consequently it is considered a poor candidate for transdermal absorption. When applied to the skin, it is absorbed in very minute quantities or not absorbed at all.

Transdermal routes for administration of anti-inflammatory agents offer various advantages over the oral route such as lower dosage, less toxicity/side effects, no G I irritation, no dose dumping in the body and it is more site specific (Chien YW: Novel Drug Delivery System, Marcel Dekker, New York, 1982).

The literature and market surveys show that at present, there exists no properly effective percutaneous formulations of Nimesulide.

In the patent for Nimesulide drug molecule (US Patent No. 3,840,597) the use of Nimesulide as an anti-inflammatory agent in the dose range of 1 mg to 500 mg per kg. body weight in the form of cream, gel, tapes and the like has been cited. According to our studies, it was observed that the drug either precipitated out in the conventional formulation or precipitated on application to human skin when applied as a conventional gel or cream in the above stated dosage and practically no percutaneous absorption occured. An over-riding difficulty is the inherent insolubility of the Nimesulide in aqueous media and hence the provision of a dosage form which can contain Nimesulide in sufficiently high concentration to permit convenient use and yet meet the required criteria in terms of bioavailability e.g. enabling effective absorption through the skin.

U.S. Patent 5,446,070 granted to Mantell et al. discloses a flexible, finite, bioadhesive composition. The present invention however, is not a finite composition or bioadhesive composition. The present invention comprises a composition which is non-finite in other words capable of being applied to large body areas for action at site of inflammation for instance the synovial fluids in joints.

Secondly, where the Mantell patent is restricted to a solvent range of 5 to 70 wt%, the solvent concentration of the present invention is upto 99.99% since the composition of the invention is a spreading non-finite composition.

Besides, unlike the Mantell et al. Patent which requires a plasticiser, a plasticiser is not required in the present invention because of its non-utility.

As regards the presence of polysaccharide, the present invention uses it along with a non-polysaccharide and the usage of a polysaccharide is at a much lower % by weight than 20% to 50% by weight as disclosed by Mantell.

Besides the polysaccharide used by Mantell in large quantities is necessary for bioadhesion which is not required in our case.

Also Mantell discloses water as an non-entity whereas in the present invention water is required in the composition.

The use of Nimesulide through intra-muscular administration as an analgesic agent has not been successful because Nimesulide is practically insoluble in water and its formulations in conventional oily bases or as suspensions result in depot formation in the muscular tissues which defies the main objective of quick relief.

The market and literature survey shows that no parenteral dosage form of Nimesulide is reported (Drugs 48 (3) 431-454, 1994).

It is an object of the present invention to provide a therapeutic composition containing Nimesulide in combination with other compounds which alter the hydrophobic property of Nimesulide, and a process for the manufacture thereof thus making it possible for the said composition to be used for direct application on the skin for the treatment of inflammation through transdermal absorption.

It is a further object of the present invention to provide a novel therapeutic composition containing Nimesulide in combination with other compounds which alter the physico-chemical properties of Nimesulide, thus making it possible for the said composition to be used for direct application to the skin for the treatment of inflammation through transdermal absorption, at dose levels much lower than the dose levels according to the known art.

SUMMARY OF THE INVENTION

The present invention provides a Novel Therapeutic Anti-inflammatory and Analgesic pharmaceutical composition for topical use which comprises :

Nimesulide	0.1% to 10% w/w
Percutaneous absorption enhancing vehicle base	90% to 99.9% w/w

The said percutaneous enhancing vehicle base acts as a microcarrier preconcentrate or a microcarrier and comprises :

Percutaneous enhancer as herein described	0.5% to 60% w/w
Surfactant as herein described	0.0% to 12% w/w
Gelling agent/Thickening agent as herein described	0.2% to 19% w/w
One or more vehicles/bases including water as herein described	5% to 97% w/w

Preferably the percutaneous enhancing base comprises :

Percutaneous enhancer as herein described.	6% to 15% w/w
Surfactant as herein described	0.5% to 12% w/w
Gelling agent/Thickening agent as herein described	0.5% to 19% w/w
One or more vehicle/base including water as herein described	5% to 60% w/w

Water is required for the composition in the range of 1% to 15% w/w, preferably 9% to 11% w/w and more preferably in the range of 9.5% to 10.5% w/w.

Besides the above disclosed ingredients the composition for topical use may also comprise a neutralising agent/pH adjusting agent such as herein described in the range of 0.0% to 2.0%.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, it has been found that it is possible to solubilise and deliver a highly hydrophobic drug like Nimesulide to the site of action through transdermal route. The present invention involves the process of incorporation of Nimesulide in a formulation which can solubilize the drug and transport it through the skin barriers, in intact condition to the site of action.

Preferably the percutaneous enhancing base comprises :

Percutaneous enhancer as herein described	6% to 15% w/w
Surfactant as herein described	0.5% to 12% w/w
Gelling agent/Thickening agent as herein described	0.5% to 19% w/w
One or more vehicles/bases including water as herein described	5% to 60% w/w

Preferably nimesulide is in the range of 1% to 5% w/w.

More preferably the composition for topical use also comprises a Neutralising agent/pH adjusting agent as herein described in the range of 0.0% to 2.0%.

The novel Therapeutic Anti-Inflammatory and Analgesic Composition for topical us according to the present invention, is prepared by a process which comprises the following steps:

(a) 0.5% to 30% w/w of a Percutaneous enhancer, as herein described, is mixed with 2.5% to 30% w/w of one or more Vehicles or bases, as herein described, in a container by stirring and to the mixture obtained 0.1% to 10% w/w of Nimesulide is added and stirred till completely dissolved.
(b) 0.5% to 12% w/w of a Surfactant, as herein described, 0.2% to 50% w/w of a Gelling agent/thickening agent, as herein described, and 2.5% to 30% w/w of one or more Vehicles/Bases, as herein described, are mixed in a homogeniser to obtain a homogenised mixture.
(c) The mixture obtained in step (a) is added to the homogenised mixture obtained in step (b) under stirring without vortex formation to avoid aeration. The mixture is neutralised or its pH adjusted by addition of 0.0% to 2.0% of a neutralising agent or a pH adjusting agent, as herein described, with slow stirring resulting in the preparation of the desired Anti-inflammatory and Analgesic Composition.

As Percutaneous enhancer any known Percutaneous enhancer may be used preferably a C_{12-24} mono or poly-unsaturated fatty acid such as vaccenic, cis-vaccenic, Linoleic, Linolenic, elaidic, oleic, petroselinic, erucic or nervonic acid and/or any of their corresponding alcohols, especially oleic acid or oleyl alcohol or 1-dodecylazacycloheptane-2-one also known as azone; sulphoxides like dimethylsuphoxide, n-decyl methylsulphoxide; Amides like dimethylacetamide, dimethylformamide and N, N-diethylm-toluamide; Pyrrolidones like 2-pyrrolidone and N-methyl-2 Pyrrolidone.

As a surfactant, any pharmaceutically acceptable hydrophilic or lipophilic surfactant or mixture thereof may be used, especially suitable for this purpose are the reaction products of natural or hydrogenated vegetable oils and ethylene glycol i.e. polyoxyethylene glycolated natural or hydrogenated vegetable oils, e.g. polyoxyethylene glycolated natural or hydrogenated castor oils; especially various tensides available under the trade name CREMOPHOR particularly CREMOPHOR RH 40 and CREMOPHOREL. Also suitable for use are the various surfactants available under the trade name NIKKOL e.g. NIKKOL HCO-60.

Polyoxyethlene Sorbitan fatty acid esters e.g. mono and trilauryl, palmityl, stearyl and oleyl esters e.g. those available under the trade name TWEEN preferably TWEEN 40 and TWEEN 80.

Polyoxyethylene-polyoxypropylene block copolymers e.g. especially those available under the trade name POLOXAMER preferably POLOXAMER 188.

Polyoxethylene fatty acid esters, for example polyoxyethylene stearic acid esters, commercially available under the trade name MYRJ as well as polyoxyethylene fatty acid esters commercially available under the trade name CEIIOL HE; Propylene glycol mono-and di-fatty acid esters such as propylene glycol dicaprylate, propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, propylene glycol stearate;

Examples of suitable lipophilic surfactants include Transesterification products of natural Vegetable oil triglycerides and polyalkylene polyols. Preferred are products obtained by trans-estrification of 2 molar parts of natural vegetable oil triglycerides with one molar parts of polyethylene glycol (e.g. having an average molecular weight of from 200 to 800). Various forms of such trans-estrification product are commercially available under the trade name LABRAFIL, preferably LABRAFIL M 1944 CS;

Sorbitan fatty acid esters commercially available under the trade name SPAN including Sorbitan monolauryl, monopalmityl, monostearyl, tristearyl, monooleyl and trioleyl esters;
Monoglycerides e.g. Glycerol monooleate, glycerol monopalmitate and glycery 1 monostearate commercially available under the trade names MYVATEX, MYVAPIEX and MYVEROL.

As Gelling Agent/Thickening agent, any known such pharmaceutically acceptable agent may be used including synthetic or semi-synthetic polymeric materials, polyacrylate and polyacrylate co-polymeric resins e.g. polyacrylic acid and polyacrylic acid/methacrylic acid resins, commercially available under the trade name CARBOPOL, particularly CARBOPOL 934, 940 and 941 and EUDRAGIT, particularly EUDRAGIT E, L, S, SL and RS;
Cellulose and cellulose derivatives including alkyl celluloses e.g. methyl-, ethyl- and propyl-celluloses; hydroxyalkyl-celluloses e.g. hydroxypropyl cellulose, hydroxypropyl alkylcellulose such as hydroxypropyl-methyl- cellulose, acylated celluloses e.g. cellulose-acetates, cellulose acetate phthalates and salts thereof such as sodium carboxymethyl cellulose;
Polyvinyl resins including polyvinylacetates and alcohols as well as other polymeric materials including alginates e.g. alginic acid and salts thereof e.g. sodium alginate and propylene glycol alginate.

As a Neutralising/pH adjusting agent any such conventional agent may be used including sodium bicarbonate, sodium hydroxide, potassium hydroxide, borax, disodium hydrogen phosphate and sodium dihydrogen phosphate.
Preferably polar organic amines like diethylamine, diisopropanolamine, triethylamine and triethanolamine may be used.

As vehicles/base, the following may be used :
Pharmaceutically acceptably lower (having C_{1-5}) alkanols, particularly ethanol; water soluble macrogols like polyethylene glycol having an average molecular weight from 200 to 600 : 1,2-propylene carbonate, propane-1,2-diol and 1,2 -propylene glycol; glycerol triacetate or (1,2,3) -triacetin; lower ketones, particularly acetone and 1,2,3 -propanetriol may

be incorporated.

Water in varying concentration may be added to provide requisite hydrophilic nature to the composition.

Pharmaceutically acceptable C_{1-5} alkyl or tetra hydrofurfuryl; di or partial ether of a low molecular weight mono or polyoxyalkanediol particularly those available under the trade names

TRANSCUTOL and COLYCOFUROL.

As base having lipophilic phase for the preparation of emulsions, may be used fatty acid triglycerides, preferably medium chain fatty acid triglycerides; vegetable oils like coconut oils, olive oil, castor oil and their derivatives; ethyl oleate.

As base, for the preparation of the said therapeutic composition in the form of an ointment, may be used fatty acids, fats, oils and waxes of animal origin like bees wax, spermacetii, wool fat, waxes of vegetable origin or mineral origin like hard, soft and liquid paraffin.

The topical dosage forms are formulated suitably such that the resultant product is easy to apply and is non-staining.

For the said therapeutic composition in the form of aerosol formulation for topical applications, as pharmaceutically acceptable propellants may be used chlorofluoro-carbons e.g. the Propellant 11, Propellant 12, Propellant 114; Hydrocarbon propellants like n-butane, isobutane and propane; compressed gas propellants e.g. Nitrous oxide, carbon dioxide, and nitrogen.

The novel therapeutic composition according to the present invention may be used in the following forms:

1. Topical aqueous gel.
2. Oil-in-water or water-in-oil emulsion or micro-emulsion or cream.
3. Solution for topical applications.
4. Ointment.
5. Aerosol formulation for topical applications.

The therapeutic composition according to the present invention may be applied on the skin by utilising a physical form of energy like electrical energy or ultrasonic energy to effect better percutaneous absorption of the drug.

The invention will now be described with reference to the foregoing examples :

Example 1

Preparation of topical gel dosage form

Sl. No.	Component	Quantity
1,	Nimesulide	2.0 g
2.	Dimethlacetamide	22.0 g
3.	Ethyl Alcohol	40.0 g
4.	Acetone	10.0 g
5.	Cremophor RH 40	4.0 g
6.	Propylene glycol	38.0 g
7.	Polyethylene glycol 400	48.8 g
8.	Carbopol 934	4.0 g
9.	Water	30.0 g
10.	Diethylamine	1.2 g
	Total	200.0 g

Step (a) Dimethylacetamide is mixed with ethyl alcohol and acetone at 30°C in a container with strring. To the mixture obtained Nimesulide is added and stirred till completely dissolved.

Step (b) Propylene glycol, polyethylene glycol 400 and water are mixed in homogenizer. To the homogenised mixture obtained, 1.5% w/w of carbopol 934 is added in small amounts at a time at room temperature and the speed of the homogenizer is kept at apporoximately 1500-2000 rpm.

Step (c) The mixture obtained in step (a) is added to the mixture obtained in step (b) under stirring without vortex formation to avoid aeration preferably under vacuum (25 mm of Hg). The mixture obtained is neutralised by slow addition of Diethylamine with slow stirring at a temperature of 25°-30°C and under vacuum (25 mm of Hg) to affect gel formation.

Example 2

Preparation of emulsion type topical dosage form.

Sl. No.	Component	Quantity
1.	Nimesulide	1.0 g
2.	Transcutol	35.0 g
3.	Water	10.0 g
4.	Disodium hydrogen phosphate	0.1 g
5.	Cremophor RH 40	5.0 g
6.	Labrafil M 1944 CS	10.0 g
7.	Glyceryl monostearate	8.0 g
8.	Stearic acid	13.0 g
9.	Ethyl oleate	2.9 g
10.	Diethyl sulphoxide	15.0 g
	Total	100.0 g

Dissolve Nimesulide in a mixture of (6), (7), (8), (9) and (10) with warming. Separately mix (2), (3), (4) and (5) and slowly add the Nimesulide mixture to it with stirring.

Example 3

Preparation of a solution type dosage form for topical application

Sl. No.	Component	Quantity
1.	Nimesulide	1.0 g
2.	Dimethyl formamide	10.0 g
3.	Poloxamer 188	2.0 g
4.	Ethyl alcohol	20.0 g
5.	Propylene glycol	25.0 g
6.	Polyethylene glycol 400	42.0 g
7.	Hydroxypropylmethylcellulose	1.0 g
8.	Triethanolamine	0.2 g
9.	Water	1.0 g
	Total	100.0 g

Nimesulide is dissolved in (2) with stirring and (3), (4), (5), (6), (7) and (8) are added to obtain a clear solution with stirring.

Example 4

Preparation of ointment type dosage form topical application.

Sl. No.	Component	Quantity
1.	Nimesulide	2.0 g
2.	Dimethylsulphoxide	21.0 g
3.	Glycerylmonostearate	16.0 g
4.	Mineral Oil	62.0 g
5.	White petrolatum	97.0 g
6.	Water	2.0 g
	Total	200.0 g

Warm (3), (4) and (5) and add with stirring a solution of Nimesulide in dimethyl sulphoxide.

Example 5

Preparation of an aerosol dosage form for topical use.

Sl. No.	Component	Quantity
1.	Nimesulide	1.0 g
2.	Dimethylacetamide	10.0 g
3.	Ethyl Alcohol	10.0 g
4.	Cremophor RH 40	10.0 g
5.	Propellant 114	29.0 g
6.	Propellant 12	39.0 g
7.	Water	1.0 g
	Total	100.0 g

The analgesic activity of the therapeutic composition, prepared according to the present invention, was found to be dose dependent and passed the tests of subacute toxicity and undue toxicity.

The dose levels of the novel Anti-inflammatory and Analgesic composition, according to the present invention, are comparatively much lower than the dose levels of the Conventional Nimesulide formulations for equally effective results.

The various forms of the therapeutic composition prepared according to the present invention were subjected to in-vitro drug release studies using modified USP dissolution apparatus attached with enhancer cell (Pharm Tech. Jan. 1995, 52-58). The dissolution media used was phosphate buffer pH 7.4. The results indicated that the cumulative drug release and permeation flux were proportional to the drug load.

The said compositions were also subjected to standard pharmacological test methods to measure anti-inflammatory activity such as rat paw oedema and guinea pig erythema. These tests showed significant activity when compared to placebo.

The said Therapeutic compositions were also tested on sixty healthy human volunteers for irritation or other side effects. No incidence of irritation/side effects was reported.

Since many apparently different embodiments of the present invention could be made without departing from the

spirit and scope thereof, it is intended that the description of the invention herein be interpreted as being illustrative only and not limiting in any manner whatsoever.

Claims

1. A Novel Therapeutic Anti-inflammatory and Analgesic pharmaceutical composition for topical use which comprises:

Nimesulide	0.1% to 10% w/w
Percutaneous absorption enhancing vehicle base	90% to 99.9% w/w

2. A pharmaceutical Composition for topical use as claimed in claim 1 wherein the said Percutaneous enhancing vehicle base acts as a microcarrier preconcentrate or a microcarrier and comprises :

Percutaneous enhancer as herein described	0.5% to 60% w/w
Surfactant as herein described	0.0% to 12% w/w
Gelling agent/Thickening agent as herein described	0.2% to 19% w/w
One or more vehicles/bases including water	5% to 97% w/w

3. A pharmaceutical composition as claimed in claim 2 which comprises:

Percutaneous enhancer as herein described	6% to 15% w/w
Surfactant	0.5% to 12% w/w
Gelling agent/Thickening agent including water as herein described	0.5% to 19% w/w
One or more vehicles/bases as herein described	5% to 60% w/w

4. A pharmaceutical composition as claimed in claim 1 which comprises a neutralising agent/pH adjusting agent in the range of 0.0% w/w to 2.0% w/w.

5. A pharmaceutical composition as claimed in claim 2 wherein said percutaneous enhancer is selected from the group comprising :

   C_{12-24} mono or poly-unsaturated fatty acids such as vaccenic, cis-vaccenic, Linoleic, Linolenic, elaidic, oleic, petroselinic, erucic or nervonic and/or any of their corresponding alcohols, especially oleic acid or oleyl alcohol or 1-dodecylazacycloheptane-2-one,; sulphoxides such as dimethylsuphoxide, n-decyl methylsulphoxide; Amides such as dimethylacetamide, dimethylformamide and N, N-diethylm-toluamide; Pyrrolidones such as 2-pyrroplidone and N-methyl-2 Pyrrolidone.

6. A pharmaceutical composition as claimed in claim 5 wherein the percutaneous enhancer is dimethylacetamide.

7. A pharmaceutical composition as claimed in claim 2 wherein the said surfactant is selected from the group comprising; any pharmaceutically acceptable hydrophilic or lipophilic surfactant or mixture thereof, the reaction products of natural or hydrogenated vegetable oils and ethylene glycol such as polyoxyethylene glycolated natural or hydrogenated vegetable oils such as polyoxyethylene glycolated natural or hydrogenated castor oils; Polyoxyethlene -Sorbitan fatty acid esters e.g. mono and trilauryl, palmityl, stearyl and oleyl esters, Polyoxyethylene-polyoxy-

propylen block copolymers, Polyoxyethylene fatty acid esters, Propylene glycol mono-and di-fatty acid esters such as propylene glycol dicaprylate, propylen glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, propylene glycol stearate; lipophilic surfactants such as transesterification products of natural Vegetable oil triglycerides and polyalkylene polyols, Sorbitan fatty acid esters, Monoglycerides such as Glycerol monooleate, glycerol monopalmitate and glyceryl monostearate.

8. A pharmaceutical composition as claimed in claim 2 wherein said gelling/thickening agent is selected from the group comprising :

Synthetic or semi-synthetic polymeric materials, polyacrylate and polyacrylate co-polymeric resins such as polyacrylic acid and polyacrylic acid/methacrylic acid resins, Cellulose and cellulose derivatives including alkyl celluloses such as methyl-, ethyl-, and propyl-celluloses; hydroxyalkyl-celluloses such as hydroxypropyl cellulose, hydroxypropyl alkylcellulose such as hydroxypropyl-methyl-cellulose, acylated celluloses such as cellulose-acetates, cellulose acetate phthalates and salts thereof such as sodium carboxymethyl cellulose; Polyvinyl resins including polyvinylacetates and alcohols as well as other polymeric materials including alginates such as alginic acid and salts thereof such as sodium alginate and propylene glycol alginate.

9. A pharmaceutical composition as claimed in claim 2 wherein water is present in the range 1% to 15% w/w.

10. A pharmaceutical composition as claimed in claim 9 wherein water is present in the range of 9% to 11% more preferably in the range of 9.5% to 10.5% w/w.

11. A pharmaceutical composition as claimed in claim 4 wherein the said neutralising agent is selected from the group comprising :

sodium bicarbonate, sodium hydroxide, potassium hydroxide, borax, disodium hydrogen phosphate and sodium dihydrogen phosphate, polar organic amines such as diethylamine, diisopropanolamine, triethylamine and triethanolamine.

12. A pharmaceutical composition as claimed in claim 2 wherein the said vehicle/base is selected from the group comprising: Pharmaceutically acceptably lower (having C_{1-5}) alkanols, particularly ethanol; water soluble macrogols like polyethylene glycol having an average molecular weight from 200 to 600 : 1,2-propylene carbonate, propane-1, 2-diol and 1,2,-propylene glycol; glycerol triacetate or (1,2,3,) -triacetin; lower ketones, particularly acetone and 1,2,3-propanetriol,
pharmaceutically acceptable C_{1-5} alkyl or tetra hydrofurfuryl; di or partial ether of a low molecular weight mono or polyoxy-alkanediol; fatty acid triglycerides, preferably medium chain fatty acid triglycerides; vegetable oils like coconut oils, olive oil, castor oil and their derivatives; ethyl oleate, fats, oils and waxes of animal origin like bees wax, spermacetii, wool fat, waxes of vegetable origin or mineral origin like hard, soft and liquid paraffin.

13. A pharmaceutical Composition as claimed in Claim 1 which is in the Form of a Topical aqueous gel.

14. A pharmaceutical Composition as claimed in claim 1 which is in the form of an oil-in-water or water-in-oil emulsion or micro-emulsion or cream.

15. A pharmaceutical Composition as claimed in Claim 1 which is in the form of a Solution for topical application.

16. A pharmaceutical Composition as claimed in Claim 1 which is in the form of an ointment.

17. A pharmaceutical Composition as claimed in Claim 1 which is in the form of an Aerosol formulation.

18. A process for the production of a therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical use which comprises the following steps :

a) mixing 0.5% w/w to 30% of a percutaneous enhancer with 2.5% to 30% w/w of one or more vehicles or bases;
b) adding to the mixture of step a), 0.1% w/w to 10% w/w of Nimesulide followed by stirring the mixture until completely dissolved;
c) mixing separately 0.5% w/w to 12% w/w of a surfactant, 0.2% w/w to 50% w/w of a Gelling agent/thickening agent and 2.5% w/w to 30% w/w of n or more vehicles or bases and mixing the entire mixtur in a homoge-

niser to obtain a homogenised mixture;

d) adding the mixture obtained in step b) to th homogenised mixture obtained in step c) under stirring to obtain the desired composition for analgesic use.

19. A process as claimed in claim 18 wherein a neutralising agent or a pH adjusting agent is added to the composition in step d) to neutralise or adjust the ph of the mixture.

20. A process as claimed in claim 19 wherein the said neutralising agent/pH adjusting agent is added in the range of 0.0% w/w to 2.0% w/w.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 4460

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	WO 96 11002 A (HISAMITSU PHARMACEUTICAL CO INC) 18 April 1996 * the whole document *	1-17	A61K9/20 A61K9/06 A61K9/08
T	& CHEMICAL ABSTRACTS, vol. 125, no. 4, 22 July 1996 Columbus, Ohio, US; abstract no. 41817, SATORU M. ET AL: "Antiinflammatory agent for external use" * abstract *	1-17	A61K9/10
X	& DATABASE WPI Section Ch, Week 9621 Derwent Publications Ltd., London, GB; Class B05, AN 96-209645 & WO 96 11002 (HISAMITSU PHARM CO LTD) , 18 April 1996 * abstract *	1-17	
X	EP 0 532 900 A (LPB ISTITUTO FARMACEUTICO S.P.A.) 24 March 1993 * page 2, line 36 - line 39 *	1	
A	JOURNAL OF CONTROLLED RELEASE, vol. 25, no. 1 / 02, 27 May 1993, pages 1-20, XP000361364 SANTUS G C ET AL: "TRANSDERMAL ENHANCER PATENT LITERATURE" * the whole document *	1-17	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
A	WO 91 17774 A (BOEHRINGER INGELHEIM ITALIA) 28 November 1991 * page 16; example 13 *	1-17	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	5 December 1996	Boulois, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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